REMARKS

Claims 1 and 3-27 are pending.

At the outset, Applicants thank Examiners Tung and Benzion for their time and thoughtful discussion during a telephonic interview conducted on June 13, 2002, with the undersigned. The substance of the interview, regarding the Passmore reference, is discussed below.

Rejections Under 35 U.S.C. 103

Claims 1, 3-12 and 15-27

Claims 1, 3-12 and 15-27 remain rejected as unpatentable over Passmore US 5,976,846. This rejection is respectfully traversed. As discussed with the Examiner, the present invention relates to a method of making a library of naturally-occurring nucleic acid inserts in vivo. All the claims include providing and introducing into each of a plurality of host cells (a) a vector molecule having a first region and a second region and (b) a different nucleic acid insert molecule in each of the plurality of cells, where the insert has a first common region homologous with the first region of the vector and a second common region homologous with the second region of the vector. The homologous first and second regions of the insert and vector homologously recombine with each other *in vivo* to provide a library of vectors, each having a different one of the originally provided inserts.

In contrast, Passmore describes a method of multifragment in vivo cloning. All of the Passmore methods require construction of a vector to be "assembled from three (or more) component parts" (Passmore 9: 41-42, emphasis added). In contrast to the claimed methods, the Passmore method results in cloned vectors that carry new sequences recombined from the 2 or more inserts introduced into the cells. Note that every figure in Passmore shows the recombination of at least 3 molecules that can only recombine together if all 3 are present. In the Passmore methods, there is no single DNA molecule (e.g., insert) having a first and second region homologous to a first and second region of a second nucleic acid molecule (e.g., vector) which is introduced into the cell, as is required in the present claims.

As discussed with the Examiners, there is no motivation or suggestion to modify the method of Passmore to provide one insert and one vector that can recombine with each other. Indeed, such a modification would defeat the purpose of the Passmore method, which is to "assemble multiple DNA fragments" (i.e., 3 or more DNA fragments) (Passmore 1:37-39). Passmore states, "Nor have any [recent reports] involved the recombination of more than two DNA fragments. Our mapping is routinely done with three pieces (the vector plus two overlapping inserts) and has also worked well with four" (Passmore 26:6-11). In reference to a method in E. Coli used to join 2 DNA molecules, Passmore states "this method can be used to join at most 2 DNA molecules; this is a significant disadvantage since it is desirable to join 3 DNA molecules" (Passmore 2:22-25, emphasis added). Passmore also states in reference to another method, also utilizing E. Coli, that "...the likelihood of efficient trimolecular and higher order recombinations would be extremely low" (Passmore 2: 54-56, emphasis added). In yet another example, Passmore recites that a method for constructing plasmids in yeast by Ma et al. "...can be used to join at most 2 DNA molecules; this is a significant disadvantage" (Passmore 3:15-16). In light of the emphasis by Passmore that their multifragment in vivo cloning confers the great advantage of allowing 3 or more molecules to be combined, there is absolutely no motivation or suggestion to modify the Passmore method to recombine 2 DNA molecules as recited in the present claims. As discussed with the Examiners, modifying Passmore's 3-way recombination method to provide 2-way recombination, i.e., inserting into a host cell an insert and vector capable of recombining with each other, would render Passmore unsatisfactory for its intended use and/or change the principle of its operation. Thus, Passmore cannot support an obviousness rejection. (See MPEP 2143.01). The prior art must suggest the desirability of the claimed invention. Instead, Passmore suggest the undesirability of 2-way recombination, clearly teaching away from the claimed methods.

Moreover, if the method of Passmore were modified to delete a restriction site, as the final office action suggests, there would sill be three fragments, not two, since Passmore does not utilize restriction enzyme sites to produce their multiple fragments. Thus, Applicants are confused about the statement in the office action that removing a restriction fragment in the Passmore method would result in Applicant's claimed methods. Further, the office action states that "it would have been obvious to substitute the two nucleic acid inserts of Passmore et al. with

another a single insert because it was routine practice in the art." As the Examiners are aware, the fact that the claimed methods may be within the capabilities of one of ordinary skill in the art is not sufficient to establish obviousness (MPEP 2143.01).

Finally, the office action states that Passmore's discussion of the disadvantages of prior art methods relates to the fact that other methods are performed in yeast. This is not the case. As discussed above, Passmore points to prior art methods using E. Coli (e.g., Stemmer, Oliner et al., Jones et al.) and yeast (e.g., Degryse et al., Ma et al., Muhlrad et al.). The prior art methods discussed by Passmore all have the same disadvantage of recombining only 2 DNA molecules regardless of the host cell system used. Thus, it is not the specific host cell system that causes the disadvantage.

Claims 13 and 14

Claims 13 and 14 are rejected in view of Passmore and Fraser. This rejection is respectfully traversed. As discussed above, Passmore does not teach or provide a motivation to arrive at the claimed methods. In fact, Passmore teaches away from the present methods. Fraser does not make up for the deficiencies of Passmore. Therefore, Applicants respectfully request that this rejection be withdrawn.

In view of the foregoing remarks, it is respectfully submitted that the application is in condition for allowance.